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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,789	11/05/2003	Victor J. Dzau	18989-028	7439

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
12/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,789	DZAU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/19/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 92-97* is/are pending in the application.

4a) Of the above claim(s) *4-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12 and 92-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 9/22/2008 are acknowledged. Claim 1 has been amended. Claims 4-11 are withdrawn from consideration. Claims 1-3, 12, 92-97 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and new grounds of rejections will not be reiterated. The arguments in 2/19/08 response would be addressed to the extent that they apply to current rejection.

Priority

In view of the persuasive argument, the priority date for the claimed subject matter as related to SDF-1 has been established as the filing date of the provisional application 60/493,874, i.e. August 8, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 96, 97 are stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et al* (US 5,993,801), and *Shake et al* (Ann Thorac Surg 2002;73:1919-26), and as evidenced by *Matsui et al* (Circulation 1999;100:2373-9).

Matsui et al teach a method for treating cardiac injury comprising administering an adenoviral vector comprising a nucleic acid encoding a constitutively active Akt via left thoracotomy into the anteroapical myocardium of cardiac ischemia model rats, and reported that Akt activation at the site of cardiac ischemia not only reduced cell death and size of the infarction, but also dramatically improved regional cardiac functions (e.g. the abstract).

Claim 1 has been amended to recite "wild type" akt gene. *Matsui et al* used a myr-akt “mutant”. However, a closer look of the structure of the myr-akt fusion protein (see Matsui 1999, page 2374, column 2), one would find the change was not on wild type akt gene, but addition of epitope tag and membrane targeting signal (myristolation was known in the art to target the expression to membrane and HA-tag was known in the art for easy detection), and hence the wild-type akt was present in the construct disclosed by *Matsui et al* and performed the same function as the wild-type akt.

Matsui et al do not teach administering a mesenchymal stem cell genetically modified to express the akt gene.

Greenberger et al remedy the deficiency by establishing it was well known in the art that bone marrow stromal cells (mesenchymal stem cells) could be used as carriers for delivering an exogenous gene to a patient in need of such transgene (e.g. claims 1 and 2).

Shake et al remedy *Matsui et al* in view of *Greenberger et al* by establishing that it was well known in the art that mesenchymal stem cells are capable of differentiating into cardiomyocytes, and thus could be used for repairing damaged cardiomyocytes. *Shake et al* transplanted MSCs to a swine myocardial infarction model, and reported "robust engraftment”, and therapeutic effect, i.e. markedly reducing the extent of wall thinning after the infarction. At the end of the experiment, i.e. *four weeks* after transplantation, the implanted MSCs could be seen in all treated animals (e.g. the abstract and figure 5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Matsui et al,* with that of *Greenberger* and *Shake et al*, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector with a reasonable expectation of

success. The ordinary skilled artisan would have been motivated to modify the claimed invention because not only MSC was a well known transgene carrier but also have the potential to directly repair/regenerate cardiomyocytes. Given that each of the cited references teaches an agent that is effective in cardiac tissue repair/regeneration and in gene transfer, one would have had a reasonable expectation of success combining the akt nucleic acid and mesenchymal stem cells. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant first argue that each of the references relied on does not teach every limitation of the claims.

Applicant's arguments have been fully considered but they are not persuasive. This is because the applicant's arguments are against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The applicant then argues that *Matsui* directly injecting the Akt gene vector into the heart, and the Akt works directly in cardiomyocytes, the teaching steers the skilled artisan away from the cells required by the instant claims.

The arguments have been fully considered but found not persuasive. This is because it was well known in the art before instant priority date a therapeutic gene of interest could be delivered either directly to the target cell of interest *in vivo* or through *ex vivo* transfected cells, and the direct *in vivo* delivery method suffers from low transduction efficiency. In fact, *Matsui* introduced the Akt gene into cardiomyocytes *in vitro*, not directly into the heart. Even so, they listed low transduction efficiency as a

reason to consider for incomplete protective effect (column 2, page 2377). Moreover, the Office cited *Shake* to establish that mesenchymal stem cells are capable of differentiating into cardiomyocytes *in vivo* upon transplantation, and thus there would be added benefit for repairing damaged cardiomyocytes.

The applicant then argue there would be no reasonable expectation of success by putting Akt in a mesenchymal cell and delivering such to myocardium because the Akt would be inaccessible to the cardiomyocytes.

In response, as indicated *supra*, the transduced MSCs would differentiate into cardiomyocytes. Further, the vectors within the MSCs are capable of transfecting adjucent cardiomyocytes upon contact, and the expressed Akt is capable of reaching adjacent cardiomyocytes. Accordingly, the Akt gene and the gene product would be accessible to the surrounding cardiomyocytes.

The applicant then argue Greenberger does not stand for a teaching that stem cells are used to deliver any exogenous gene, the role of the cells in Greenberger is to produce and secrete.

In response, produce and secrete is a means for deliver an exogenous gene to the recipient. Although the exemplified gene may be FVIII and TGF, the claims certainly embrace any biologically active mammalian protein (see e.g. claim 1). Although Greenberger does not teach implanting the cell to a heart tissue, it would have been obvious to the skilled in the art in view of *Shake*, who teaches implanting MSCs into heart tissue. The Supreme court stated, "IF A TECHNIQUE HAS BEEN USED TO IMPROVE ONE DEVICE, AND A PERSON OF ORDINARY SKILL IN THE ART WOULD RECOGNIZE THAT IT WOULD IMPROVE

SIMILAR DEVICES IN THE SAME WAY, USING THE TECHNIQUE IS OBVIOUS UNLESS ITS ACTURAL APPLICATION IS BEYOND THAT PERSON'S SKILL" (*KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. at 1740, 82 USPQ2d at 1395-96, see particular page 4 of Syllabus) Here, using the MSCs for delivering an exogenous gene and for repairing damaged cardiomyotes were known in the art, and it would have been obvious to combine such to arrive at instantly claimed invention.

The applicant then argues Dr. Shake indicated there are no need to pretreat MSCs.

In response, in the context of the entire paragraph cited by the applicant, the referred pretreatment is directed to induce lineage differentiation, not whether they are capable of carrying a therapeutic gene of interest. "[O]THER INVESTIGATORS ARE CERTAINLY TRYING TO SEND SKELETAL MYOBLASTS OR MSCS DOWN LINEAGES. WE HAVE SEEN THAT IF JUST INJECTED INTO THE RIGHT ENVIRUONMENT, THE MSCS DIFFERENTIATE INTO WHAT THEY SHOULD BE IN THAT ENVIRONMENT" (Last paragraph, column 1, page 1926).

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claims 12 and 92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberge r et al* (US 5,993,801), and *Shake et al* (Ann Thorac Surg 2002;73:1919-26)as applied to claims 1-3, 96, 97 above, and further in view of *Palasis et al* (US 2002/0172663), for reasons of record and *supra*.

Claims 12, 92-95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Matsui et al* (Circulation 2001;104:330-5), in view of *Greenberger et al* (US 5,993,801), and *Shake et al* (Ann Thorac Surg 2002;73:1919-26) as applied to claims 1-3, 96, 97 above, and further in view of *Penn et al* (US 2004/0037811), for reasons of record and *supra*.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI, M.D.** whose telephone number is **571-**

272-0730. The examiner can normally be reached on 9 AM -7:00pm, Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633

QJL
December 16, 2008